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PCBs Disturb Differentiation of Normal Human Neural Progenitor Cells: Clue for Involvement of Thyroid Hormone Receptors.

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Running title: PCBs disturb differentiation of NHNP cells.

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A conflict of interest was not reported.

Abbreviations:

AhR arylhydrocarbon receptor

AhRR AhR repressor

CYP cytochrome P450

GFAP glial fibrillary acidic protein

GST glutathione-S-transferase

NHNP cells normal human neural progenitor cells

NSE neuron specific enolase

PCB polychlorinated biphenyls

RA retinoic acid

RAR retinoic acid receptor

RXR retinoic x receptor

T_3 triiodothyronine

TH thyroid hormone

TR thyroid hormone receptor

UGT UDP glucuronosyl transferase

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Abstract

Polychlorinated biphenyls (PCBs) are ubiquitous environmental chemicals that accumulate over the food chain in adipose tissues. Epidemiological studies have indicated that PCBs influence brain development. Children who are exposed to PCBs during their development suffer from neuropsychologic deficits such as a lower full-scale IQ, reduced visual recognition memory, attention and motor deficits. The mechanisms leading to these effects are not fully understood. It has been speculated that PCBs may affect brain development by interfering with thyroid hormone (TH) signaling. Since most of the data have been gained from animal studies, we established the model of primary normal human neural progenitor cells (NHNP cells) to analyze if PCBs interfere with TH dependent neural differentiation.

NHNP cells differentiate into neurons, astrocytes and oligodendrocytes in culture. They express a variety of drug metabolism enzymes and nuclear receptors. Like triiodo thyronin (T_3), treatment with the mono ortho substituted PCB118 (0.01 – 1 μM) leads to a dose dependent increase of oligodendrocyte formation. This effect was congener specific, since the coplanar PCB126 had no effect. Similar to the T_3 response, the PCB mediated effect on oligodendrocyte formation was blocked by retinoic acid (RA) and thyroid hormone receptor (TR) antagonist NH-3. These results suggest that PCB118 mimics T_3 action via the TH pathway.